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Genetics and prospective therapeutic targets for Sjögren-Larsson Syndrome

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Abstract

Introduction—Sjögren-Larsson syndrome (SLS) is a rare neurocutaneous disease characterized by ichthyosis, spasticity, intellectual disability and a distinctive retinopathy. It is caused by inactivating mutations in *ALDH3A2*, which codes for fatty aldehyde dehydrogenase (FALDH) and results in abnormal metabolism of long-chain aliphatic aldehydes and alcohols. The potential disease mechanisms leading to symptoms include 1) accumulation of toxic fatty aldehydes that form covalent adducts with lipids and membrane proteins; 2) physical disruption of multi-lamellar membranes in skin and brain; 3) abnormal activation of the JNK cell signaling pathway; and 4) defective farnesol metabolism resulting in abnormal PPAR-α dependent gene expression. Currently, no effective pathogenesis-based therapy is available.

Areas Covered—The clinical, pathologic and genetic features of SLS are summarized. The biochemical abnormalities caused by deficient activity of FALDH are reviewed in the context of proposed pathogenic mechanisms and potential therapeutic interventions.

Expert Opinion—The most promising pharmacologic approach to SLS involves blocking the formation of potentially harmful fatty aldehyde adducts using aldehyde scavenging drugs, currently in phase 2 clinical trials. Other approaches needing further investigation include: 1) ALDH-specific activator drugs and PPAR-α agonists to increase mutant FALDH activity; 2) inhibitors of the JNK phosphorylation cascade; 3) antioxidants to decrease aldehyde load; 4) dietary lipid modification; and 5) gene therapy.

Keywords

Aldehyde dehydrogenase; aldehyde scavenging drugs; fatty alcohol; fatty aldehyde; ichthyosis; intellectual disability; spasticity

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1. Introduction

Sjögren–Larsson syndrome (SLS) is an inherited neurocutaneous disease characterized by ichthyosis, spastic diplegia or tetraplegia, intellectual disability and a distinctive retinopathy. [1–3] It is caused by mutations in *ALDH3A2*, which codes for fatty aldehyde dehydrogenase (FALDH) [4] and results in abnormal lipid metabolism.[5] SLS is inherited as an autosomal recessive trait and has an estimated prevalence of about 1 in 250,000. Although first described in a cohort of patients in northern Sweden [1], it has now been seen worldwide and in all ethnic groups.[2,3]

The current therapy of SLS is limited to general measures for treating the cutaneous and neurologic symptoms as they arise. Although specific therapeutic agents for SLS have not reached standard clinical practice, efforts to develop targeted drugs have recently emerged based on a better understanding of the genetic etiology, disrupted lipid pathways and the pathogenic mechanisms in play. In this paper, I review the clinical, genetic and biochemical features of SLS and provide opinion on the most promising therapeutic approaches for this orphan disease.

2. Clinical features

The cutaneous abnormality of SLS is the first clinical sign to be noted. Affected infants are usually born with an erythematous, hyperkeratotic skin that transforms over days to the dry scaly appearance of ichthyosis.[6] The entire body is affected with relative sparing of the central face. Older infants and children often have disturbing pruritus, which may manifest as excessive excoriations, sometimes with bleeding. Motor milestones are typically affected in the first 2 years of life because of spasticity.[1–3] Delays in onset of sitting, crawling and/or walking are the rule. Patients typically exhibit spastic diplegia, which impairs their ability to ambulate independently although many patients eventually walk with the assistance of leg braces and canes. Tetraplegia is much less common. Most patients have intellectual disability, but cognitive impairment can vary from severe to mild or more rarely normal intelligence.[2,3] Onset of speech is also delayed and dysarthria is commonly present.[7] One or more seizures occur in about 40% of SLS patients.[2] A distinctive retinal abnormality characterized by macular degeneration with perifoveal crystalline inclusions, so called glistening white dots, develops in the first few years of life.[8] Patients have an unusual deficiency of macular pigment [9] and thinning of the retinal layers.[10] Photophobia is common and mild visual impairment is usually corrected with glasses. Despite these many symptoms, life expectancy is not severely reduced and most patients survive into adulthood.[2,3]

The prominent neurological symptoms in SLS are associated with abnormal magnetic resonance imaging (MRI) of brain. Patients demonstrate an increased T2-weighted signal intensity in myelin that chiefly involves the periventricular regions.[11] These changes develop within the first several years of life. In addition, magnetic resonance spectroscopy (MRS) detects abnormal lipid peaks at 0.9 and 1.3 ppm in cerebral white matter, which may contribute to the abnormalities seen on MRI.[11–13] The chemical nature of the lipids is not known, but their spectra are consistent with fatty alcohols or other aliphatic molecules.[13]

A detailed neuropathological report of a genetically confirmed SLS patient has not been published, but investigations of unconfirmed patients indicate non-specific loss of myelin in the central nervous system, including the spinal cord, with histological features of gliosis, astrocyte proliferation, ballooning of the myelin sheaths and the presence of macrophages with myelin-breakdown products.[14,15]

Article highlights

- Sjögren–Larsson syndrome (SLS) is a rare genetic disease characterized by ichthyosis, intellectual disability, spasticity and a distinctive maculopathy.
- SLS is caused by mutations in *ALDH3A2* that result in deficient activity of fatty aldehyde dehydrogenase (FALDH) and abnormal long-chain aldehyde metabolism.
- The pathogenic mechanisms are likely related to formation of fatty aldehyde adducts with lipids and proteins and/or accumulation of fatty alcohol and related lipids, which disrupt critical membranes, interfere with cell signaling and/or alter gene expression.
- Prospective therapeutic approaches include use of aldehyde trapping agents to block adduct formation (currently in phase 2 clinical trials), pharmacologically enhance residual FALDH activity, modulate cell-signaling pathways, restrict dietary intake of aldehyde-related lipids and decrease toxic aldehydes generated by oxidative stress.
- Gene therapy for SLS is a future goal that must address the need for multi-organ gene replacement or correction.

This box summarizes the key points contained in the article.

Histologic studies of the skin in SLS reveal hyperkeratosis, papillomatosis, epidermal hyperplasia, and acanthosis.[16] Ultrastructural studies demonstrate an abnormal formation of cytoplasmic lamellar bodies in the stratum granulosum. [17,18] These defective vesicular structures contain granular material and lack the usual cargo membranes that are normally secreted in the space between the stratum granulosum-stratum corneum and assemble into multi-lamellar membranes in the stratum corneum. Consequently, intercellular stratum corneum membranes are structurally abnormal and functionally unable to prevent water loss through the skin, resulting in reactive hyperproliferation of the epidermis and hyperkeratosis. [18]

3. Genetics of *ALDH3A2*

3.1. ALDH3A2 gene structure and transcriptional regulation

The *ALDH3A2* gene is located on chromosome 17p11.2 and spans 31 kb in size. The gene consists of 11 exons.[19] Alternative splicing gives rise to two major protein isoforms that differ in length and subcellular localization. The major protein isoform of FALDH consists

of 485 amino acids and is localized to the endoplasmic reticulum (ER) by its carboxy-terminal domain.[20] The minor isoform (FALDH*v*), which accounts for <10% of the total protein, consists of 508 amino acids [19] and is targeted to peroxisomes.[21] This dual subcellular localization of FALDH serves to metabolize aldehyde substrates generated during lipid metabolism in the ER and peroxisomes. In mice, the relative amounts of the two splicing variants differ slightly among tissues.[22] Small amounts of other mRNA splicing variants of unknown significance have been detected in some mammalian cells.[21]

FALDH is considered a housekeeping protein that is constitutively expressed in all tissues and nucleated cells.[19,22] However, animal studies have shown that certain drugs and physiological conditions influence the expression of the gene. In rodents, *Aldh3a2* is upregulated by insulin and downregulated in diabetes.[23] The *Aldh3a2* gene has a peroxisome proliferator activated receptor-α (PPAR-α) response element in the promoter and is transcriptionally induced by PPAR agonists including fibrate drugs [24,25], dietary phytol [26], dietary sesame seeds [21], and certain fatty acids such as linoleic acid [25] and branched-chain fatty acids (phytanic acid and pristanic acid).[27] It is assumed that the human *ALDH3A2* gene is subject to similar regulatory control, but studies involving the tissues most affected in SLS, skin and brain, have not been reported.

3.2. ALDH3A2 mutations in SLS

More than 80 mutations in *ALDH3A2* have been reported in SLS patients.[28–37] These include missense mutations, small deletions and insertions, splice site mutations and complex rearrangements. Larger deletions involving one or more exons in *ALDH3A2* have also been detected [30] along with contiguous gene deletions in chromosome 17p.11.2 involving multiple flanking genes.[31]

About one-half of patients carry homozygous mutations that tend to be private.[28,29] Several common mutations have been identified in patients from Europe [28,29,35,38], the Mideast [28], Brazil [39] and Honduras.[37] Haplotype studies indicate that they probably represent founder effects and inbreeding. However, several recurrent mutations have also arisen independently.[28,35]

Missense mutations comprise approximately 38% of the known *ALDH3A2* mutations.[29] Most of these have been expressed in Chinese hamster cells or insect cells and found to produce FALDH proteins with no detectable catalytic activity. Several missense mutations, however, encode FALDH proteins that possess 1–9% of normal catalytic activity.[28,29] Because of the many mutations and limited number of genotyped patients, it is not yet possible to clearly establish genotype–phenotype correlations in this disease. Nevertheless, some patients with the same ALDH3A2 mutation have shown divergent clinical severities suggesting the presence of modifier genes or environmental influences on the disease. [37,40,41]

4. Biochemical defect

FALDH (also called ALDH3A2) is one member of a larger family of aldehyde dehydrogenase (ALDH) enzymes in man, which differ in substrate specificity, nucleotide

cofactor preference and subcellular localization.[42,43] FALDH uses NAD+ as nucleotide cofactor to irreversibly oxidize aliphatic aldehydes to fatty acids. It is catalytically active as a homodimer consisting of two 54 kD subunits.[44] The enzyme has broad substrate specificity and will act on C6–C24 aldehydes, including monounsaturated, polyunsaturated and methyl-branched aldehydes.[45] Notably, retinal is not a substrate for the enzyme.

FALDH has recently been crystallized and its 3-dimensional structure solved.[46] The protein has a unique 'gatekeeper' domain that consists of a hydrophobic helix that covers the substrate entry tunnel to the catalytic site and enhances the preference for long-chain aldehydes. The structural location of most of the known missense mutations have been mapped to the functional domains of the protein, allowing detailed predictions about their effects on protein catalysis, dimerization and folding.[46]

FALDH deficiency in SLS results in impaired oxidation of fatty aldehydes derived from several lipid pathways [5] (Figure 1). These include long-chain aldehydes generated by the enzymatic degradation of ether glycerolipids (including plasmalogens) [47]; sphingosine-1-phosphate [48]; α-oxidation of phytanic acid [49]; and ω-oxidation of leukotriene B4 (LTB4) [50] and very long-chain fatty acids.[51] Lipid peroxidation during oxidative stress results in production of a number of medium- and short-chain aliphatic aldehydes, including the highly reactive 4-hydroxy-2-nonenal (4-HNE), which is a substrate for FALDH. Given its central role in aliphatic aldehyde metabolism, it is likely that aldehydes derived from other lipid pathways will be ultimately implicated in SLS.

The defective metabolism of fatty alcohol to fatty acid was the first abnormal biochemical pathway identified in SLS.[52] Long-chain alcohols are generated from fatty acids through the fatty alcohol cycle, which provides alcohol substrate for synthesis of ether glycerolipids and wax esters (see Figure 1). Excess fatty alcohol is recycled back to fatty acid through a metabolic process that requires two enzymatic steps catalyzed sequentially by fatty alcohol dehydrogenase (FADH) and FALDH (Figure 1). These two enzymatic activities are present on separate membrane-bound proteins that work together to comprise fatty alcohol : NAD oxidoreductase (FAO).[53,54] During oxidation of fatty alcohol to fatty acid, the fatty aldehyde intermediate appears to be tightly bound to FAO, suggesting that FADH and FALDH are physically close in the ER membrane. The physical interaction between FADH and FALDH is not yet established because attempts to purify FAO have been stymied by loss of FADH activity.[54] Kinetic studies in normal fibroblasts suggest that the first step in long-chain alcohol oxidation is rate limiting because the apparent Km for FAO is lower than that for FALDH alone.[55] Owing to deficient FALDH in SLS, FAO activity is impaired and C16–C18 alcohols accumulate.[56,57] In contrast, shorter chain alcohols do not seem to accumulate, suggesting that other ALDH enzymes are capable of oxidizing these substrates normally. Furthermore, branched-chain isoprenols (farnesol and geranylgeraniol) are poorly oxidized to their corresponding acids in cultured SLS fibroblasts, indicating that FALDH acts on aldehydes derived from these alcohols.[58]

5. Pathogenic mechanisms

Development of pharmacologic approaches for the treatment of SLS will be largely dictated by knowing the pathogenic mechanisms responsible for the tissue dysfunction in this disease. The genetic basis of SLS is clearly established, but understanding the exact pathogenic mechanisms is still a major challenge. Several lipid abnormalities are implicated, but it is not yet possible to separate the effects of one lipid from the total array of changes. [5,59] Indeed, multiple biochemical mechanisms may be operating in SLS, some of which may be more tissue-specific for skin or nervous system. This is highlighted by the striking differences seen between cultured skin fibroblasts and keratinocytes in their lipid pathways and response to FALDH/FAO deficiency.[60] It is anticipated that brain-derived cells have their own unique response to FALDH deficiency. Moreover, the severity of the ichthyosis does not seem to correlate with the neurologic deficits in SLS [61], suggesting that pathogenic mechanisms may differ in these tissues.

5.1. Fatty aldehyde toxicity

The FALDH defect and the generally toxic nature of aldehydes point to accumulation of fatty aldehydes as most likely to contribute to the pathogenic mechanisms in SLS. Aldehyde toxicity has been demonstrated in a number of cellular systems and with a wide range of aldehyde molecules.[62,63] The reactive nature of aldehydes permits a variety of chemical interactions with other molecules resulting in the formation of covalent bonds between the aldehyde carbonyl group and other reactive chemical groups in lipids, proteins or other molecules.[62] Most aldehydes can readily form Schiff base adducts with the ε-amino group of protein-bound lysine. Certain α,β-unsaturated aldehydes and 4-alkenals are particularly reactive because of their electrophilic nature and have a propensity to form Michael adducts with cysteine and histidine.[62,63] To date, however, very few studies have focused on the toxic effects of the longer chain aldehydes (C16–C18) that are seen in SLS.[64,65] Because of their lipophilic properties, long-chain aldehydes are expected to partition into membranes of various intracellular compartments, most notably the ER and peroxisomes where FALDH is located.

Several membrane lipids are potential targets for aldehyde modification. The most abundant target involves the amino group of phosphatidylethanolamine (PE), a major phospholipid of most biological membranes. Additional amino-containing lipids include sphingosine, sphingosine-1-phosphate and phosphatidylserine. Long-chain aldehydes (C16–C18) can also attack the galactosyl moiety of glycolipids by formation of cyclic acetal (plasmal) adducts resulting in plasmalocerebroside [66], plasmalopsychosine [67], and plasmalogalactosyl-1-*O*-alkylglycerol [68], which have been detected in normal human and equine brain. With exception of PE, however, aldehyde adducts with these lipids have not yet been reported in SLS.

Long-chain aldehyde adducts can be detected in cultured SLS fibroblasts and mutant FALDH-deficient Chinese hamster ovary (CHO) cells.[64] In these cells, the addition of fatty aldehydes to the culture medium resulted in formation of the Schiff base product, N-alkyl-PE. Accumulation of this lipid adduct was much greater in the FALDH-deficient cells compared with wild-type cells. When fatty aldehyde was produced endogenously from

metabolism of radioactive 1-*O*-alkylglycerol, SLS fibroblasts accumulated fourfold more radioactive N-alkyl-PE than control cells.[47] Moreover, mutant CHO cells [64] and cultured human keratinocytes from SLS patients [65] were found to be more sensitive to the cytotoxic effects of fatty aldehydes compared with wild-type cells. The addition of a hydrophobic long-chain alkyl group to the hydrophilic ethanolamine moiety of PE is expected to have profound effects on its interactions with membranes and membrane-associated proteins. Although considerable levels of N-alkyl-PE were achieved in the mutant CHO cells treated with fatty aldehyde [64], it is not known whether enough N-alkyl-PE accumulates in the skin and brain of SLS patients to have detrimental effects. Rather than being directly responsible for membrane dysfunction, N-alkyl-PE may instead be a biomarker of the metabolic defect that reflects aldehyde adducts in general.

Membrane proteins are attractive targets for fatty aldehydes, which could thereby exert effects on a variety of metabolic pathways. Although all membrane proteins are potential targets for aldehyde adduct formation, certain proteins may be particularly susceptible. For example, myelin basic protein (MBP), which is the second most abundant protein in myelin, is highly enriched in lysine residues. MBP has been shown to interact *in vitro* with artificial membrane vesicles containing hexadecanal.[69] A potential metabolic source of long-chain aldehydes in myelin includes plasmalogen forms of PE, which comprise up to 90% of the total phospholipids of myelin.[70] Long-chain aldehydes are produced during the enzymatic degradation of plasmalogens.[71] During oxidative stress, oxygen free radicals react with the vinyl ether bond in plasmalogens to release fatty aldehydes.[72,73] The resultant aldehydes would likely accumulate in SLS myelin membranes and react with MBP, PE and other potential targets. This raises the intriguing hypothesis that aldehyde-modified MBP, N-alkyl-PE and plasmalolipids formed in SLS myelin are responsible for the changes seen on MRI/MRS and neurologic symptoms in SLS patients (Figure 2). MBP alterations are expected to have detrimental effects on compacting myelin membranes, linking cytoskeletal proteins to myelin and altering oligodendrocyte cell signaling.[74] Furthermore, mutations in this protein are known to cause dysmyelinating diseases in mice [75] and heterozygous deletion of the *MBP* gene in humans is associated with dysmyelination.[76]

5.2. Sphingosine-1-phosphate metabolism

Sphingosine-1-phosphate is a metabolic product of sphingolipids and has an important role in intracellular cell signaling. [77] Degradation of sphingosine-1-phosphate by sphingosine-1-phosphate lyase releases *trans*-2-hexadecenal, which is oxidized by FALDH to *trans*-2-hexadecanoic acid.[48] Studies in cultured mammalian cells have recently shown that *trans*-2-hexadecenal added to the culture medium induces cell rounding and apoptosis through a cell signaling mechanism involving a phosphorylation cascade with MLK3, MKK4/7 and JNK (c-Jun N-terminal kinase) [68] (Figure 3). JNK activation also requires reactive oxygen species. JNK is one of the mitogen-activated protein kinases (MAPK) that are activated by various stimuli through different coupled receptors such as G-protein-coupled receptors, receptor tyrosine kinases, Ser/Thr kinase receptors and cytokine receptors.[78] How *trans*-2-hexadecenal initiates the JNK phosphorylation cascade and whether the JNK signaling pathway can be affected by other fatty aldehydes are not known. Although studies confirming aberrant JNK activation in SLS cells have not yet been

reported, the JNK finding links fatty aldehyde accumulation to a cell-signaling pathway that may contribute to the myelin abnormality in SLS (Figure 2). It also raises questions about fatty aldehyde effects on other signaling pathways.

5.3. Epidermal ceramide deficiency

Ceramides comprise a major lipid in the stratum corneum and are important for integrity of the epidermal water barrier, epidermal cell signaling and apoptosis. Two reports have identified a reduction in ceramide-1 (1-*O*-acyl-ceramide) in cutaneous scales for SLS patients.[79,80] Ceramide-1 is unique to the skin and structurally differs from most other ceramides by incorporating linoleic acid in acyl linkage with the ω-carbon of the very long-chain fatty acid portion of ceramide.[81] Nutritional linoleic acid deficiency is associated with a defective epidermal water barrier and cutaneous desquamation, which is thought to be because of reduced acyl-ceramide. Profound reductions of acyl-ceramide and other ceramides in skin are caused by genetic knockout of the ELOVL4 enzyme that is responsible for very long-chain fatty acid elongation, and results in ichthyosis and neonatal lethality in mice.[82,83] Although the metabolic link between reduced acyl-ceramide (ceramide-1) and FALDH deficiency is not known, this biochemical alteration in stratum corneum may contribute to the ichthyosis in SLS.

5.4. Straight-chain fatty alcohol accumulation

SLS patients accumulate C16:0 and C18:0 straight-chain alcohols in plasma and cultured cells.[56,57] In cultured SLS keratinocytes, excess fatty alcohol is diverted into biosynthetic pathways for wax esters and ether glycerolipids, which also accumulate. [60] It has been hypothesized that accumulation of these lipids within the epidermal keratinocytes of SLS patients is responsible for the lamellar body membrane abnormalities seen in the stratum granulosum and the resulting water barrier defect associated with ichthyosis.[18] Experimental evidence that straight-chain fatty alcohols are specific pathogenic drivers for the ichthyosis in SLS skin, however, is still lacking.

5.5. Disrupted isoprenol metabolism

Isoprenols (farnesol and geranylgeraniol) are biologically active lipids that affect keratinocyte differentiation [84], calcium channels [85,86], cell signaling through prenylated rab proteins [87] and apoptosis.[88] In SLS fibroblasts, farnesol and geranylgeraniol are poorly oxidized to farnesoic acid and geranylgeranoic acid, respectively.[58] Defective metabolism of these isoprenols and/or their phosphorylated metabolites (i.e. farnesyl-PP) could have potential detrimental effects. Farnesol increases the degradation of HMG-CoA reductase and decreases synthesis of cholesterol [89], a major membrane lipid in the stratum corneum and brain. Treatment of rodents with topical lovastatin, an inhibitor of HMG-CoA reductase results in an ichthyotic phenotype.[90] This raises the possibility that impaired farnesol oxidation might cause defective cholesterol synthesis and/or protein prenylation and cell signaling. Farnesol also activates PPAR-α and induces expression of keratinocyte differentiation genes. [84] With deficient oxidation of farnesol in SLS cells, it is possible that altered PPAR-α activation results in abnormal gene expression resulting in aberrant keratinocyte differentiation.

5.6. Leukotriene B4 accumulation

SLS patients have defective ω-oxidation of LTB4, a lipid inflammatory mediator synthesized from arachidonic acid.[50] Urinary LTB4 and 20-hydroxy-LTB4 are highly elevated in SLS patients because of a block in FALDH-dependent oxidation of LTB4 to its 20-carboxy degradation product. In animal experiments, LTB4 induces intense pruritus when injected subcutaneously [91], suggesting that the pruritus in SLS may be because of LTB4 accumulation in skin.

6. Prospective therapeutic targets and interventions

Understanding the biochemical abnormalities in SLS provides a roadmap for the development of therapeutic interventions. Owing to the involvement of FALDH in oxidizing lipids derived from several pathways, there is no dearth of potential therapeutic targets for SLS. However, our inability to pinpoint a specific lipid that is primarily responsible for one or more symptoms means that biochemical approaches to this disease are in part exploratory and hypothesis testing at this time. Pharmacologic approaches to modulate gene expression or biochemical pathways affected in SLS are under investigation, whereas more direct therapies involving gene replacement in multiple tissues remain a challenging goal. Table 1 summarizes the past, current and potential future therapeutic approaches for SLS.

6.1. Block fatty aldehyde adduct formation with aldehyde trapping agents

To combat aldehyde toxicity, attempts have been made to use small molecules to compete as sacrificial targets for endogenously produced aldehyde, thereby protecting susceptible cellular molecules.[92] These aldehyde scavengers include several hydroxylamine derivatives and amino-containing small molecules.[93–95] Aldehyde trapping agents are non-discriminate in their function, potentially reacting with a wide range of aldehydes and protecting a spectrum of intracellular target molecules. If the symptoms in SLS are caused by formation of aldehyde adducts with key proteins or lipids, aldehyde-trapping agents should theoretically be beneficial. Proof of principle for the protective effect of amino-containing drugs has recently been demonstrated using a mouse model of retinal-induced damage to visual function.[96] A variety of small molecules containing primary amines were found to have the ability to prevent retinal pathology that was induced by excessive all-*trans*-retinal.

In SLS, potential aldehyde scavengers should be lipophilic to readily enter intracellular membranes where fatty aldehydes are produced. Preliminary *in vitro* studies have demonstrated the effectiveness of stearylamine to block N-alkyl-PE formation in cultured SLS fibroblasts, but this aliphatic amine was associated with cytotoxicity (unpublished). The non-toxic drug NS2 (2-[3-amino-6-chloro-quinolin-2-yl]-propan-2-ol; Aldeyra Therapeutics, Lexington, MA, USA) has the ability to react with hexadecanal and competitively inhibit formation of N-alkyl-PE in microsomal membranes from mouse liver. When added to cell culture medium, NS2 lowered N-alkyl-PE in FALDH deficient CHO cells.[97] Based in part on these studies, a phase 2 clinical trial of topical NS2 was recently initiated for the ichthyosis in SLS (www.clinicaltrials.gov). With a topical agent such as NS2, it is expected that high levels of the drug should be achieved in skin. For treating the neurologic symptoms

of SLS, however, aldehyde-trapping agents will need to be administered systemically and probably begun early in the course of the disease before neurologic symptoms become irreversible.

6.2. Stimulate ALDH3A2 gene expression with PPAR agonists

Some *ALDH3A2* missense mutations in SLS result in a protein with a small amount of residual enzyme activity.[28,29] Using cultured fibroblasts from patients carrying these mutations, Gloerich et al. [98] found that bezafibrate, a PPAR-α ligand, stimulated transcription of the mutant *ALDH3A2* gene and significantly increased residual enzyme activity. To date, the clinical application of bezafibrate or other PPAR activating drugs in SLS has not been reported, so their *in vivo* efficacy in this disease remains unclear.

6.3. ALDH activators to enhance residual FALDH enzymatic activity

Small molecules that increase activity of ALDH enzymes and protect against aldehyde toxicity in animals have recently been developed.[99,100] These activators appear to function in part as chemical chaperones by stabilizing the enzyme from denaturation [101] or binding to the enzyme active site and influencing catalysis.[102] One compound, Alda-89 (5-allyl-1,3-benzodioxol) was found to selectively stimulate FALDH (ALDH3A2) activity by threefold *in vitro* while having minimal effect on other ALDHs.[100] Infusion of Alda-89 into mice for 7 days resulted in a 29% increase in esophageal enzyme activity. In SLS patients having a mutant enzyme with some residual activity, an ALDH3A2 activator could be beneficial by increasing enzyme activity. Although promising, ALDH activators and chemical or pharmacologic chaperones have not yet been explored in SLS.

6.4. Inhibit lipid peroxidation with antioxidants

Overexpression of FALDH protects cultured cells from the toxic effects of 4-hydroxynonenal generated during oxidative stress [103] and during ER stress induced by phytanic acid [21] and linoleic acid.[25] However, the relative contribution of FALDH to these processes under physiologic conditions is not known. Nevertheless, if aldehydes derived from lipid peroxidation accumulate in SLS, the use of antioxidants may be a useful therapeutic approach to reduce their production.

6.5. Modulate keratinocyte differentiation with retinoids and vitamin D analogs

Systemic retinoids have a powerful effect on improving the skin in most forms of ichthyosis [104], including SLS.[105–107] They act through interaction with intracellular retinoid receptors to modulate gene expression, alter keratinocyte proliferation and differentiation and affect cutaneous scale cohesion. [108,109] Systemic retinoids, however, have potentially deleterious side effects on serum lipids and bone growth and can induce birth defects during pregnancy.[110] Most systemically administered retinoids are stored in adipose tissue and persist for long periods of time after their discontinuation. These concerns have limited their widespread chronic use in SLS. In contrast, the shorter acting retinoid acitretin has been successfully used in SLS [107], although experience is limited. Off label use of topical tazarotene, a retinoid prodrug, is also effective for treating limited areas of the skin in other forms of ichthyosis.[111] Topical calcipotriol has the ability to differentiate keratinocytes

and improve ichthyosis [112], but concerns about secondary hypercalcemia arise when used with widespread topical application. Although effective on the skin, none of these drugs impact the neurologic symptoms in SLS.

6.6. Modulate sphingosine signaling pathway

The finding that *trans*-2-hexadecenal derived from sphingosine-1-phosphate catabolism stimulates the JNK signaling pathway [113] suggests that modulation of this pathway may be a useful therapeutic approach. Several pharmacologic targets exist. Alteration of sphingosine-1-phosphate metabolism itself or inhibiting sphingosine-1-phosphate lyase to reduce *trans*-2-hexadecenal production lack specificity and may have widespread detrimental consequences on other signaling pathways. Moreover, it would not address the possibility that additional fatty aldehydes also activate JNK signaling. A focused approach targeting JNK activation seems more logical. In this regard, small molecule and peptide inhibitors of JNK activation are under development and have proven beneficial in several *in vivo* animal model systems.[114]

6.7. Replace cutaneous lipids

The stratum corneum membranes that constitute the epidermal water barrier in the skin have a critical lipid composition consisting of equimolar amounts of ceramide, cholesterol and free fatty acids. Disrupting this lipid ratio has detrimental effects and leads to ichthyosis in other lipid disorders.[115] In addition to acyl-ceramide deficiency, it has been speculated that the SLS skin may be deficient in fatty acids because of the block in oxidation of fatty alcohols to fatty acids.[116] If the lipid composition of the stratum corneum is abnormal because of deficiency of these lipids, topical application of the lipids may improve the epidermal water barrier and benefit the skin. Lotions containing generic ceramides are widely available, but these ceramides are not derived from skin and therefore lack the key acyl-ceramide lipid. A topical lotion consisting of an optimal lipid mixture has not been tried in SLS patients, although one group reported a slight improvement in the skin of SLS patients using topical cholesterol and lovastatin.[117]

6.8. Decrease fatty alcohol accumulation

Reduction in tissue fatty alcohols and/or their lipid metabolic products may be therapeutically important in SLS. Biochemical or pharmacologic approaches for mitigating accumulation of fatty alcohols by enhancing their breakdown or inhibiting their production have not been explored. The biosynthetic pathway for production of fatty alcohols, which are substrates for the synthesis of ether plasmalogen lipids, is subject to metabolic regulation.[5] Under normal physiologic conditions, the production of fatty alcohol is determined by activity of its biosynthetic enzyme, fatty acyl-CoA reductase (FAR1). Through a mechanism of feedback regulation, FAR1 activity is down-regulated by ether glycerolipids resulting in reduction of fatty alcohol synthesis.[118] Dietary treatment of SLS with supplemental ether lipids might theoretically decrease fatty alcohol production beyond that possible through its normal feedback inhibition. However, degradation of ether lipids themselves releases fatty aldehyde (Figure 1), which requires FALDH for further oxidation [47] and might lead to excess aldehyde production, negating any potential benefit. Moreover,

severe inhibition of FAR1 is expected to be detrimental, as genetic deficiency of this enzyme results in serious neurologic symptoms.[119]

6.9. Inhibit LTB4 synthesis or LTB4 receptors

Willemsen et al. have treated SLS patients with zileuton, which blocks LTB4 synthesis and lowers levels of this lipid.[120] In an open label trial, 3 of 5 SLS patients exhibited reduced pruritus and improved behavior. However, in a subsequent randomized double-blind placebo-controlled crossover study of 10 patients, only one patient showed a favorable response to zileuton.[121] This drug also did not affect the ichthyosis or neurologic symptoms. An alternate approach to pharmacologically block LTB4 receptors with small bioactive molecules may be more fruitful.[122]

6.10. Modify dietary fat

Several anecdotal reports have described improvement in the ichthyosis when SLS patients were placed on a fat modified diet.[123–127] In some cases, patients were given a diet that eliminated all animal fats and added medium-chain triglycerides.[123,124] The diets were not well described. In other cases, the diets included medium-chain triglycerides and restricted fat but were supplemented with essential fatty acids.[125–127] Clinical results have been inconsistent and no convincing effects were reported on the neurologic symptoms. Alternate dietary strategies might include dietary restriction of fatty aldehydes, fatty alcohols and aldehydogenic lipids such as plasmalogens. Little is known, however, about the dietary contribution of these lipids to total body fatty aldehydes or alcohols.

Finally, the branched-chain aliphatic lipids phytanic acid and its alcohol precursor phytol are derived solely from dietary sources (i.e. dairy products) and are metabolic precursors to the fatty aldehyde pristanal. Pristanal is normally oxidized by FALDH.[49,128,129] Dietary restriction of phytanic acid and phytol has not been investigated in SLS. It is evident, however, that phytanic acid and/or pristanal do not account for the ichthyosis in SLS, which develops before infants begin consuming these lipids. Moreover, neither phytanic acid nor phytol is elevated in plasma from SLS patients, suggesting that they are unlikely to contribute to the neurologic disease.

6.11. Gene therapy

Replacement or correction of the defective *ALDH3A2* gene is the Holy Grail for SLS and other genetic diseases. Nevertheless, efforts toward gene therapy for this disease are in their infancy. Haug et al. [130] transfected SLS keratinocytes grown in culture with *ALDH3A2* cDNA using an adeno-associated viral vector and found that the cells exhibited improved resistance to fatty aldehyde toxicity and demonstrated reduced hyperkeratosis in keratinocytes grown as skin equivalent cultures.[65]

7. Expert opinion

A number of potential therapeutic targets for SLS have been identified, but prioritizing these targets for further development will depend in part on greater understanding of the pathogenic mechanisms that lead to the symptoms of this disease. At the present time, a

single lipid pathway or abnormality that is responsible for all symptoms in SLS has not been identified and it is possible that several lipids in combination are involved. The relative contribution of the many lipid pathways that feed into FALDH is not known. Moreover, the lipid pathways within tissues, such as the stratum corneum and myelin, are not identical and may dictate unique therapeutic approaches that are tailored to each pathway and tissue. For example, if oxidative stress generates a significant aldehyde load for SLS, the use of antioxidant drugs may be beneficial, or if plasmalogen turnover in myelin is a major contributor of fatty aldehyde, drugs that inhibit this process may need to be designed.

It seems logical that fatty aldehydes, being the most proximal lipid defect and having known cellular toxicity, contribute to the disease pathogenesis to some extent, either by forming adducts with key cellular molecules, activating apoptosis, interfering with membrane protein function or through some undiscovered mechanism. This tentative conclusion provides a compelling rationale for the investigation of aldehyde trapping agents, which indiscriminately block a wide range of aldehydes that may be generated from multiple aldehyde pathways. The recently initiated clinical trial of NS2 is a first step. Nevertheless, many questions remain to be answered about this approach. What becomes of the trapped fatty aldehyde and how is it eliminated from the cell? Are reversible Schiff base adducts involved? If so, how are they stabilized? Can trapping agents be preferentially directed to critical sub-cellular sites, for example the ER, where aldehydes are generated? Are there endogenous molecules (possibly PE?) that mitigate fatty aldehyde toxicity by protecting more susceptible molecular targets?

It may be argued that the systemic use of aldehyde trapping agents is an unrealistic therapeutic approach because of the stoichiometric amounts needed to trap all potential aldehydes and prevent widespread adduct formation. However, a clinical response may not require lowering fatty aldehydes completely, especially if aldehyde levels are only marginally elevated above a critical threshold or pathogenic mechanisms involve a limited number of exquisitely susceptible molecular targets.

If symptoms in SLS arise from accumulation of fatty alcohols and/or their metabolic lipid products (alkyl-diacylglycerol and wax esters), drugs will need to be developed to inhibit FAR1 activity or fatty alcohol-dependent biosynthetic pathways. Alternately, selective dietary restriction of fatty alcohols and aldehydes might be considered if the dietary contribution of these lipids is significant.

For those patients with susceptible missense mutations, pharmacologic approaches aimed at inducing overexpression of the mutant FALDH or improving its conformational state with chaperone therapy seem promising. Unfortunately, much of what we know about pharmacologic agents that induce *ALDH3A2* expression is solely based on *in vitro* cell studies. Animal investigations of PPAR-α ligands, such as bezafibrate, have not focused on the organs that are functionally disrupted in SLS, particularly skin and brain. Whether drugs such as ALDH activators and chemical or pharmacologic chaperones have sufficient *in vivo* impact on these tissues is yet to be seen. Similarly, studies of drugs that improve splicing efficiency in SLS patients who have splice-site mutations have not been explored.

The initial *in vitro* cell studies of gene therapy for SLS have demonstrated proof-of-principle and need to be extended further. The clinical application of gene therapy will require pre-clinical studies in an animal model of the disease to show *in vivo* efficacy and safety. *Aldh3a2*−/− mice have been genetically engineered, but they exhibit minimal symptoms of ichthyosis and no overt neurologic disease (unpublished observations). Thus, a better animal model of SLS is needed before gene therapy can fully advance. A major challenge for this approach also includes the need to efficiently express normal FALDH enzyme in multiple organs (skin, brain, eye).

As more is learned about the biochemical basis for the symptoms in SLS, new therapeutic targets will undoubtedly emerge and relegate some of those discussed here to lower priority. In the absence of a single pathogenic mechanism for SLS, it is likely that effective treatment will require a combination of therapeutic interventions.

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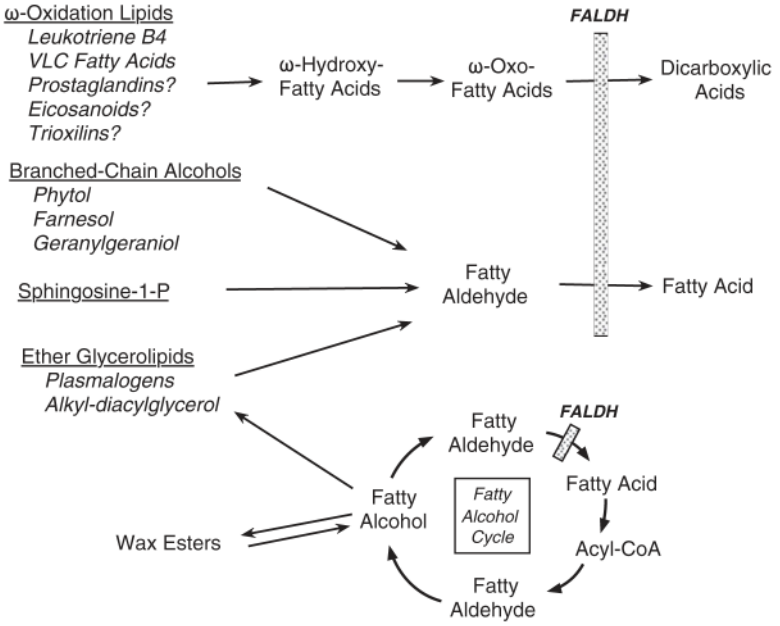

Figure 1.

Metabolism of fatty aldehydes and the role of FALDH in their oxidation. Reprinted with permission from Biochim Biophys Acta 2014;1841(3):377–89 [5].

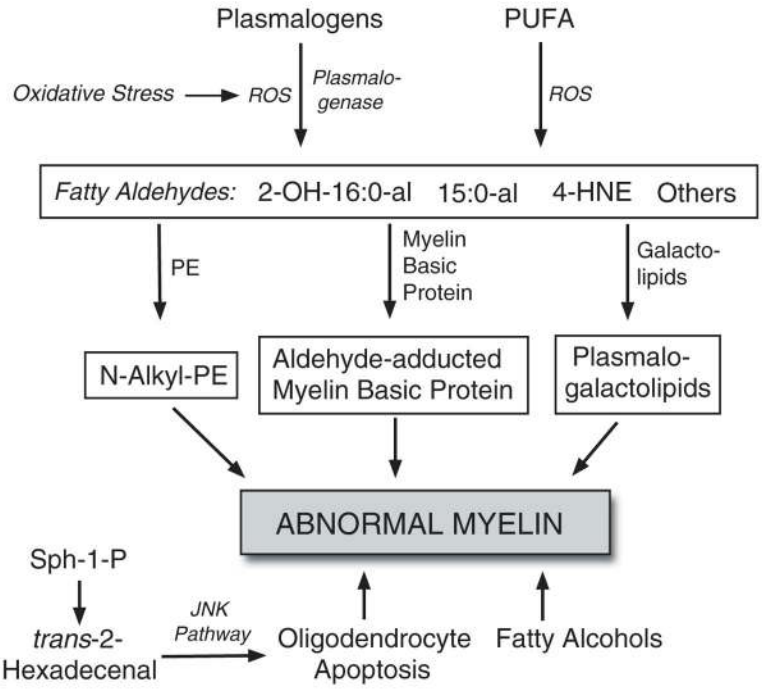

Figure 2.

Proposed mechanism for myelin abnormality in SLS. 2-OH-16:0-al, 2-hydroxy-hexadecanal; JNK, c-Jun N-terminal kinase; 15:0-al, pentadecanal; 4-HNE, 4-hydroxy-2-nonenal; PE, phosphatidylethanolamine; N-alkyl-PE, N-alkyl-phosphatidylethanolamine; ROS, reactive oxygen species; Sph-1-P, sphinosine-1-phosphate.

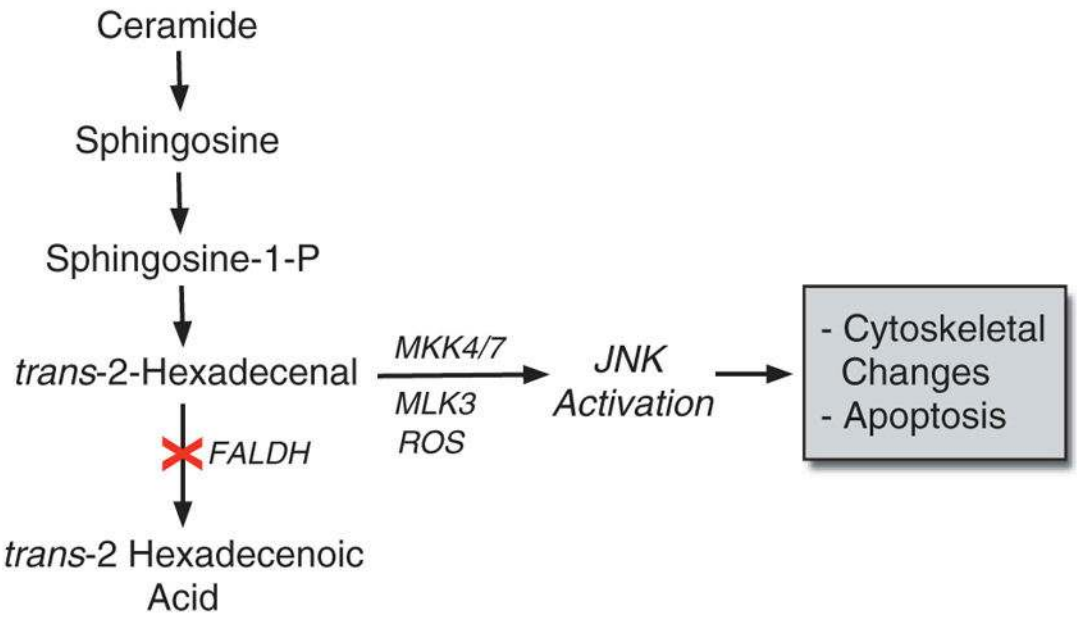

Figure 3.
Sphingosine-1-phosphate pathway leading to JNK activation. JNK, c-Jun N-terminal kinase.

Table 1

Therapeutic approaches for SLS.

Therapeutic approach	Mechanism of action
Aldehyde trapping agents	Block formation of fatty aldehyde adducts with key cellular targets
Stimulate gene expression using PPAR-α ligands	Increase synthesis of mutant FALDH enzymes with residual enzyme activity
Aldehyde dehydrogenase activators	Act as chemical or pharmacologic chaperones to increase mutant FALDH activity
Antioxidants	Decrease lipid peroxidation and reduce formation of toxic fatty aldehydes
Retinoids/topical calcipotriol	Modulate keratinocyte differentiation to improve ichthyosis
Inhibitors of JNK cell signaling	Block JNK phosphorylation cascade to decrease apoptosis
Replace cutaneous lipids	Restore acyl-ceramide and/or fatty acids in the epidermis with topical lipids to improve epidermal water barrier
Decrease fatty alcohol synthesis	Use oral ether glycerolipids or pharmacologic agents to down-regulate FAR1 enzyme and decrease fatty alcohol synthesis
Inhibit LTB4 pathway	Block LTB4 synthesis and/or LTB4 receptors to treat pruritus
Dietary fat modification	Restrict dietary sources of fatty alcohol and fatty aldehyde
Gene therapy	Replace or correct the defective *ALDH3A2* gene